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Case report

Relapse of herpes simplex encephalitis in a patient with metastatic small cell lung cancer following scalp sparing whole brain radiotherapy

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ABSTRACT

Herpes simplex virus is the most common cause of severe and potentially fatal sporadic encephalitis worldwide. Recurrence of neurologic symptoms after resolution of the initial episode of HSV encephalitis and despite adequate treatment with intravenous acyclovir is well recognized albeit rare. Most of these recurrences had no evidence of replicating virus and are immune in nature with only a minority of these recurrences representing true virologic relapses. Immunocompromised patients are predominantly at greater risk for virologic relapse of HSV encephalitis with potentially severe and at times fatal consequences. We describe a patient with small cell lung cancer and brain metastasis who underwent chemotherapy, treatment with dexamethasone and whole brain radiotherapy who subsequently suffered two episodes of HSV encephalitis three months and seven months after completion of radiotherapy and while on dexamethasone treatment.

Introduction

Herpes simplex virus (HSV) is the most common cause of severe and potentially fatal sporadic encephalitis worldwide [1] with an incidence of approximately 2–4 cases per million per year [2]. The typical presentation of Herpes simplex encephalitis (HSE) consists of decreased consciousness (90%), fever (80%), and focal neurologic deficits (70%) [3]. Clinical presentation, brain MRI and CSF analysis are the foundations of diagnosis of HSE including relapses [3].

Prior to the availability of acyclovir, mortality from HSE was unacceptably high (70%) [4]. Currently, 30-day mortality from HSE ranges between 5% and 10% whereas 20% of survivors suffer a severe neurologic sequel [4]. The pathology of HSE is a necrotizing, hemorrhagic, inflammatory encephalitis in the mesiotemporal, inferofrontal, and insular cortices, with grey matter being affected more than white matter [5]. Early diagnosis and treatment of HSE including relapses is critical to favorable clinical outcome [6] with current guidelines recommending treatment of HSE with intravenous acyclovir at a dose of 10–12 mg/kg given every 8 h for 2–3 weeks [7]. The role of corticosteroids on the neurological outcomes in patients with HSE is unknown. A randomized trial comparing acyclovir plus placebo vs acyclovir plus dexamethasone was ended due to insufficient enrollment [8].

As larger numbers of patients survived HSE, it became apparent that 10%–25% of survivors experience relapse or recurrence of neurologic symptoms despite adequate treatment with intravenous acyclovir [9]. Interestingly, most of these "relapsed" cases had no evidence of replicating virus neither in brain tissue nor viral DNA in CSF, suggesting an immune-mediated mechanism accounting for the recurrences of neurologic symptoms [10]. It is now believed that antibody against the N-methyl-D-aspartate receptor (NMDAR) is key factor in the pathogenesis of neurologic symptoms following recovery from the initial episode of HSE resulting in an autoimmune neurologic relapse [11] suggesting that only a minority (<5%) of adequately treated adult patients with HSE experience a "true" virologic relapse [12] making it a rare clinical entity.

It is believed that virologic relapse in HSE is a consequence of reactivation of a latent HSV in the trigeminal or olfactory root ganglia whereas first HSE episodes follow viral ascent from oral sites via the trigeminal or olfactory nerves in HSV-1 and from genital sites via sacral nerve roots in HSV-2 [5]. It has been observed that reactivation of latent HSV infection leading to

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virologic relapse of HSE may follow immunosuppression [13], chemoradiation [14], and deep brain stimulation among others [15].

Clinical or neuroradiological relapse in patients with previous HSE intuitively necessitates distinguishing between virologic relapse (reflected by a positive PCR for HSV in CSF) and an immune-mediated condition (such as anti-NMDA receptor encephalitis) since therapeutic approaches to these two conditions largely differ with antiviral therapy for the former and immunotherapy for the latter [16]. The use of PCR for the detection of HSV DNA in CSF is considered the gold standard for the diagnosis of HSE. It is "however" not known whether the sensitivity of PCR in detecting HSE relapses is equivalent to its sensitivity in primary HSE [17].

We describe a patient with small cell lung cancer and brain metastasis who underwent chemotherapy, treatment with dexamethasone and whole brain radiotherapy who subsequently suffered two episodes of HSE three months and seven months after completion of radiotherapy and while on dexamethasone treatment.

Case presentation

A 72-year-old man presented with a three-day history of fever, somnolence and new-onset seizure. Sixteen months prior to current presentation, he was diagnosed with metastatic small cell lung cancer for which he received chemotherapy [cisplatin and etoposide] and chest radiotherapy. A year later, he was found to have a solitary metastatic brain lesion for which he underwent scalp sparing palliative whole brain radiotherapy (30 Gy given in 10 fractions over 2 weeks) which he completed three months prior to this presentation. He was continued on dexamethasone at a dose of 4 mg daily.

Physical examination revealed a sick looking, obtunded man with positive signs of meningeal irritation. Glasgow coma scale was 13/15. Pupils were reactive, equal and of normal size. Prévost

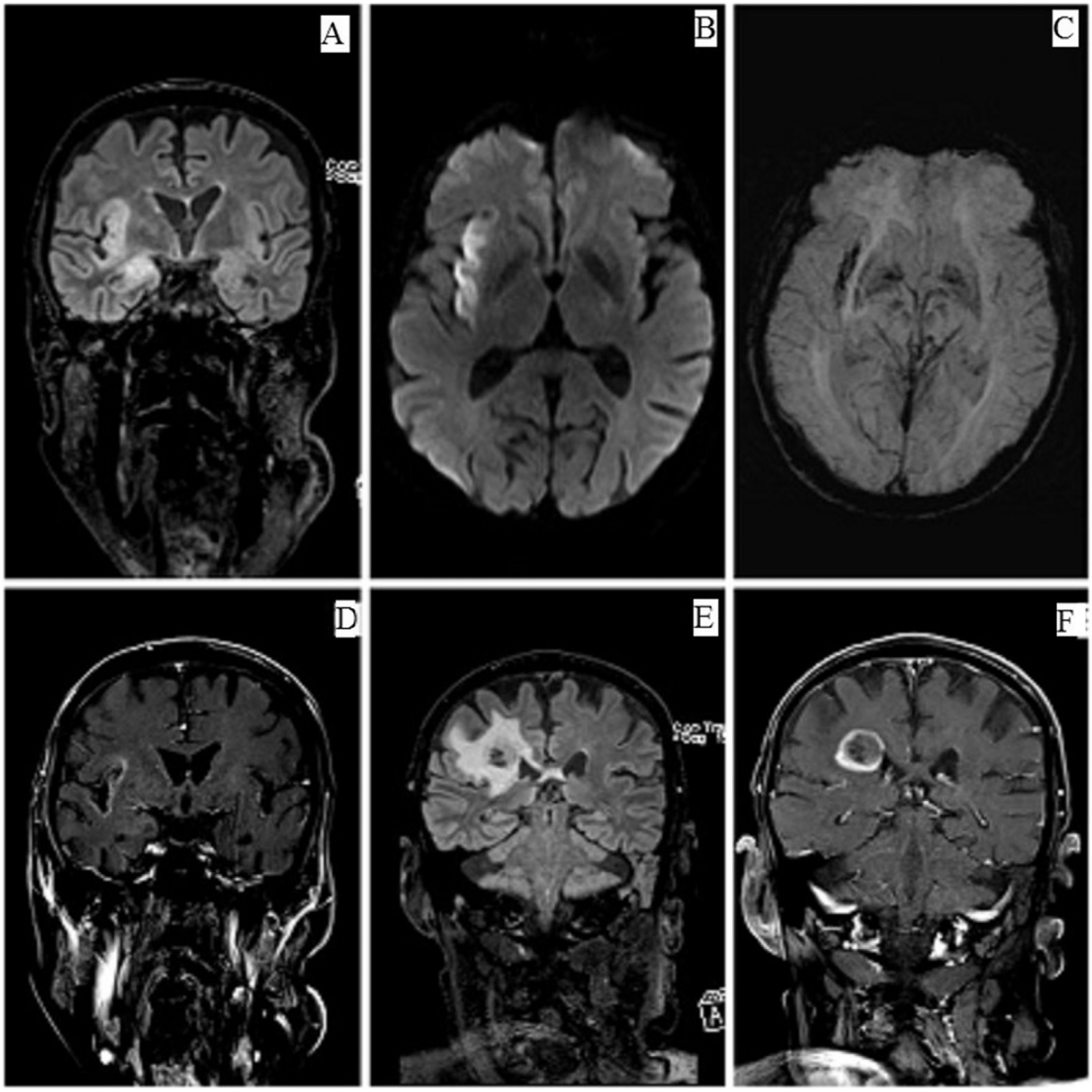

Fig. 1. (A–F): Brain MRI images at first presentation with HSV encephalitis.
A: FLAIR coronal image demonstrating gyral oedema and hyperintensity predominantly involving the right insular cortex and the right medial temporal lobe. Fig. 1B: Diffusion weighted axial image showing a linear area of hyperintensity involving the right insular cortex suggestive of diffusion restriction. Fig. 1C: Susceptibility weighted axial image revealing presence of petechial haemorrhage in the right insular cortex. Fig. 1D: Post gadolinium T1W coronal image demonstrating mild patchy gyral enhancement in the insular cortex. Fig. 1E and F: A rounded rim enhancing lesion with marked perilesional vasogenic oedema is shown at the right centrum semiovale keeping with the known brain metastasis from small cell lung cancer.

sign (deviation of the eyes away from the hemiparesis in acute cortical hemiparetic stroke) was positive with right-sided gaze. Paratonia of all four limbs was demonstrated with signs of left hemiparesis. He was febrile (38.4^{0}C), normotensive but tachycardic (116/min) and tachypneic (21/min). Oxygen saturation was 98% (room air). No skin rash. Rest of examination was normal. His condition rapidly worsened with increasing seizures and he became unresponsive requiring urgent endotracheal intubation and mechanical ventilation. He was transferred to the intensive care unit with a presumptive diagnosis of right hemispheric stroke (complicating metastatic brain lesion) and meningoencephalitis and the following antimicrobials were empirically given: ceftriaxone 2 g iv q12 h, ampicillin 2 g iv q4h, and acyclovir 12 mg/kg iv q8h. Additionally, intravenous levetiracetam (1000 mg q12 h) was administered.

Initial laboratory investigations were normal except for mild thrombocytopenia [131,000/μL] and lymphopenia [500 /μL]. Brain MRI was performed (Fig. 1).

Cerebrospinal fluid (CSF) examination showed clear fluid with 16 cells/μL (100% lymphocytes). CSF protein and glucose were 77 mg/dL and 67 mg/dL (blood glucose: 144 mg/dL) respectively. Herpes simplex virus (HSV) DNA was detected by PCR analysis of CSF. Subsequently, CSF culture showed no growth.

A diagnosis of HSV meningoencephalitis and left-sided stroke complicating brain metastasis with secondary seizures was made. The patient was continued on intravenous acyclovir (12 mg/kg q8h) for three weeks during which dexamethasone continued at 4 mg/day. He made slow recovery with improving consciousness and cognition in addition to resolution of seizures. He was discharged home tracheostomized and with major functional disability resulting from residual left-sided hemiparesis. He was continued on levetiracetam (1500 mg po q12 h) and dexamethasone (2 mg po q12 h) at time of discharge. A repeat CSF analysis was not done prior to discharge.

Four months later, he presented again with a-two-day history of fever, worsening level of consciousness, and seizures. Physical examination revealed a tracheostomized, encephalopathic man with Glasgow coma scale of 10/15. Pupils were reactive, equal and of normal size. Signs of previous left hemiparesis were again demonstrated. He was febrile (39.0^{0}C), normotensive but bradycardic (61/min) and tachypneic (19/min). Oxygen saturation was 92% (room air). There was no rash and the rest of examination was normal. Initial laboratory investigations were normal except for a hemoglobin of 6.4 g/dL, platelet count of 145,000 /μL, and absolute lymphocyte count of 900 /μL. MRI brain (Fig. 2) and EEG (Fig. 3) are depicted below.

A repeat CSF examination showed clear fluid with 5 cells/μL (100% lymphocytes). CSF protein was 106 mg/dL and CSF glucose was 80 mg/dL (blood glucose: 200 mg/dL). Herpes Simplex Virus (HSV) DNA was again detected by PCR analysis of CSF. Autoimmune encephalitis including anti-NMDA receptor antibodies and paraneoplastic screen panels in CSF were both negative.

A diagnosis of relapse of herpes simplex encephalitis was made and the patient was treated with intravenous acyclovir (12 mg/kg q8h) for three weeks. Despite treatment, the patient neurological condition worsened and remained in coma until his death four weeks after admission.

Discussion

Virologic relapse in HSE remains a rare clinical entity [12] and is infrequently reported. Furthermore, late relapse of HSE, defined as recurrence more than three months after the first initial encephalitic episode, is rarer [18]. We believe this case represents late virologic relapse of HSV culminating in second episode of HSE four months after primary HSE. Our proposition is supported by near complete resolution of the neurological symptoms associated with the first presentation on antiviral therapy, four months of symptom-free period, and second positive HSV PCR coinciding with recurrence of compatible clinical, radiological and electroencephalographic correlates. Like this patient, all documented cases of HSE, albeit primary infection, following brain radiotherapy were notable for absent or minimal CSF cell count [19]. In this case, CSF cell count was 16 cells/μL and 5 cells/μL in first and relapse presentation respectively.

There are several plausible explanations, although poorly understood, for virologic relapse of HSE some of which apply to this patient. Several anecdotal reports suggest an association between suboptimal dosing and relatively shorter duration of acyclovir therapy with relapse of HSE [20]. This is unlikely explanation in this case where intravenous acyclovir was administered at adequate dosing (12 mg/kg q8hr) and duration

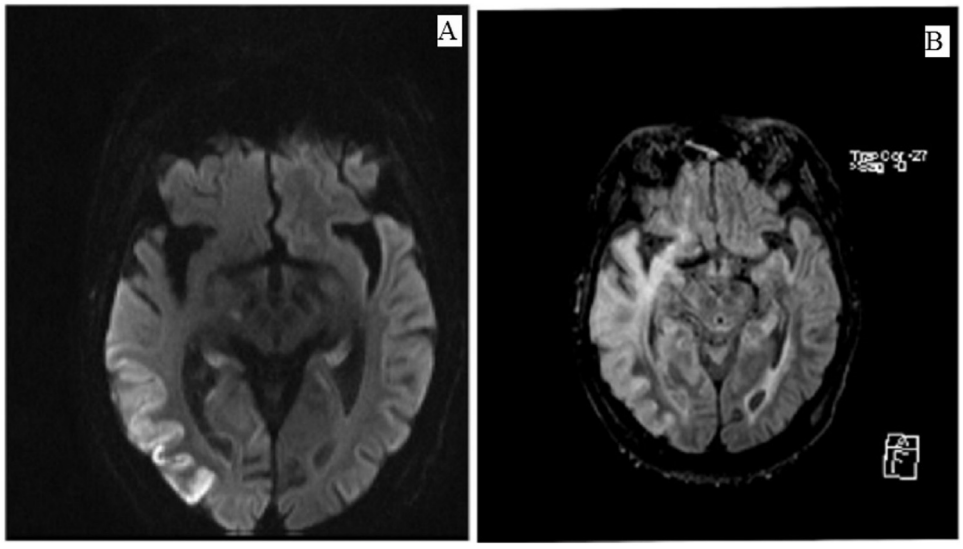

Fig. 2. (A and B): Brain MRI images at time of relapse of HSV encephalitis.
A: Diffusion weighted axial image revealing new cortical signal abnormality with diffusion restriction involving the right inferior temporal gyrus and both hippocampi. Fig. 2B: FLAIR axial image demonstrating worsening of the right temporal lobe hyperintensity compared to the previous MRI.

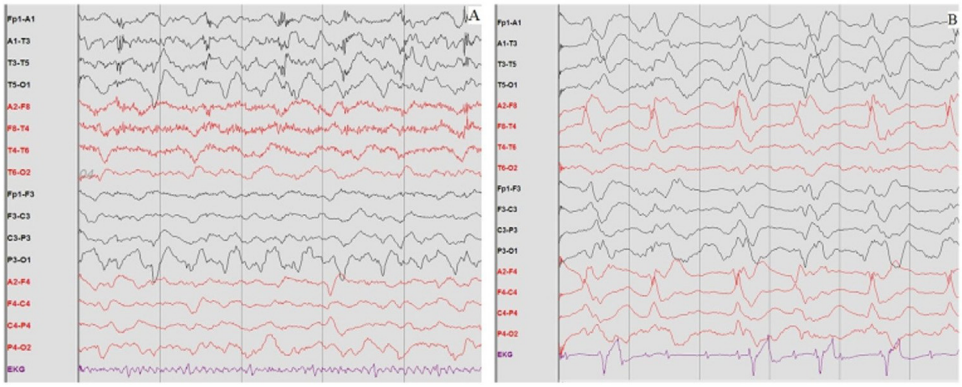

Fig. 3. (A and B): Electroencephalographic (EEG) at presentation with relapse of HSV encephalitis.
A: EEG recording demonstrating frequent left posterior temporal periodic lateralized epileptiform discharges (PLEDS) characteristic of HSV encephalitis. Fig. 3B: EEG recording showing PLEDS arising from left temporal and right frontal, temporal, and parietal lobes.

(three weeks). Immunocompetent patients with HSV encephalitis will typically have a negative CSF HSV PCR after 14 days of acyclovir treatment [18]. It is known that immunocompromised patients may fail to completely suppress or fully eradicate HSV from CSF hence they are presumed to be at greater risk for relapse of HSE [21]. Evidence of "virologic cure" after completion of treatment of the first presentation is lacking in this case. Hence possible contribution of this to clinical relapse in this case cannot be ascertained.

Incidence of primary HSE in cancer patients treated with prior whole brain radiotherapy is reportedly significantly higher in comparison to the general population with reported incidence of 1:250 and 2–4:1 million respectively [2] and the association between brain radiotherapy and HSE is well documented even though limited to approximately thirty reports [22]. Contrarywise, the association of whole brain radiotherapy with virologic relapse of HSE is largely unknown. In this patient settings, palliative scalp sparing whole brain radiotherapy was administered for metastatic brain lesion following which (3 months later) he presented with first episode of HSE. We believe that exposure to brain radiotherapy contributed to this patient vulnerability for primary HSE in agreement with published literature. Moreover, we propose that whole brain radiotherapy predisposed this patient to virologic relapse of HSE four months after the first episode.

Dexamethasone might pose a risk for relapse of HSE as suggested by a systematic review [23]. This patient was prescribed dexamethasone for relief of symptoms related to brain metastasis. He was on 4 mg daily concomitant with brain radiotherapy and up until the first presentation and 8 mg daily between the first and the second presentations with HSE. Dexamethasone, we believe, was a likely culprit for predisposing this patient to primary and recurrent HSE. It is therefore evident that this patient had several potential predispositions to relapse of HSE including underlying cancer, chemotherapy, whole brain radiotherapy and dexamethasone.

To our knowledge, there are no studies evaluating the potential role of antiviral prophylaxis for the prevention of relapse of HSE. Until this is done, we suggest that patients at risk for HSE relapse [like this patient] warranted consideration for oral suppressive antiviral therapy. Recently, a placebo-controlled study showed that oral valacyclovir (2 g q8h) given for three months post HSE did not improve neurologic outcome [24]. This study unfortunately did not evaluate the impact on virologic relapse.

We believe that virologic relapse of HSE may be underestimated and misdiagnosed. Given the potential serious consequences of relapse of HSE, at-risk immunocompromised patients receiving dexamethasone or whole brain radiotherapy may be considered for prophylactic antiviral therapy during and for an extended period following completion of treatment. Recurrence of symptoms or new neurological deficits should raise concern for HSV viral relapse.

Patient consent

Patient consent was not required for this publication.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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First/corresponding author was responsible for the writing and revising the manuscript, second author contributed to the first draft of the manuscript, and all authors contributed to the clinical care of the patient and to the revision of several drafts before submission.

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